

ATTORNEY'S DOCKET NO.: B0801/7116 (ERG/KA)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Toshimichi Shinohara, Dhirendra Singh and Leo T. Chylack, Jr.
Serial No.: 09/121,211
Filed: July 23, 1998
For: LENS EPITHELIAL CELL DERIVED GROWTH FACTOR
Examiner: D. Romeo
Art Unit: 1646
Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on the 11th day of February, 2000.

By: Edward R. Gates
Edward R. Gates

Sir:

TRANSMITTAL

Transmitted herewith are the following:

- ☒ Letter
- ☒ January 24, 2000 Office Action

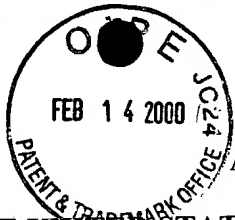
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Respectfully Submitted,

Edward R. Gates
Edward R. Gates, Reg. No. 31,616
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210
Tel. (617) 720-3500

Attorney's Docket No.: B0801/7116 (ERG/KA)
Date: February 11, 2000
XNDD

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By: _____

Edward R. Gates

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

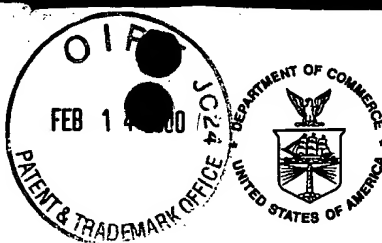
LETTER

Pursuant to Konstantinos Andrikopoulos' telephone conversation with Examiner Romeo on February 10, 2000, enclosed please find the January 24, 2000 Office Action for the above-identified application. As noted in said telephone conversation, the Detailed Action portion of this Office Action does not correspond with that of the above-identified application (U.S.S.N. 09/121,211). We look forward to receiving the complete January 24, 2000 Office Action and a recalculation of the due date. Applicants would like to thank the Examiner for his attention to this matter.

Respectfully submitted,

Edward R. Gates, Reg. No. 31,616
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210
Tel. (617) 720-3500

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/121,211 07/23/98 SHINOHARA T B0801/7116

HM22/0124

EDWARD R. GATES
WOLF, GREENFIELD & SACKS
600 ATLANTIC AVENUE
BOSTON MA 02210

EXAMINER

ROMEO, D

ART UNIT

PAPER NUMBER

1646

DATE MAILED:

10
01/24/00

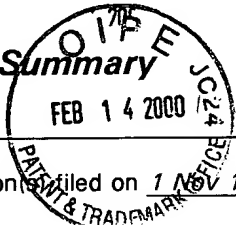
Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

04/24/00

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Office Action SummaryApplication No.
09/121,211Applicant(s)
Shinohara et al.Examiner
David S. RomeoGroup Art Unit
1646☒ Responsive to communication filed on 1 Nov 1999☐ This action is **FINAL**.☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims☒ Claim(s) see the attached detailed action is/are pending in the application.Of the above, claim(s) see the attached detailed action is/are withdrawn from consideration.☐ Claim(s) _____ is/are allowed.☒ Claim(s) 1, 3-11, and 26 is/are rejected.☒ Claim(s) 2 is/are objected to.☒ Claims see the attached detailed action are subject to restriction or election requirement.**Application Papers**☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.☐ The drawing(s) filed on _____ is/are objected to by the Examiner.☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.☐ The specification is objected to by the Examiner.☐ The oath or declaration is objected to by the Examiner.**Priority under 35 U.S.C. § 119**☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been☐ received.☐ received in Application No. (Series Code/Serial Number) _____.☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).**Attachment(s)**☒ Notice of References Cited, PTO-892 ✓☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6 ✓☐ Interview Summary, PTO-413☐ Notice of Draftsperson's Patent Drawing Review, PTO-948☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

1. Applicant's election of group I, claims 1 and 8-16 in Paper No. 5 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP

5 § 818.03(a)).

2. The preliminary amendments filed 04/05/99 (Paper No. 5) and 10/19/99 (Paper No. 10) have been entered. Claims 1, 8-16, 18-42 are pending.

3. Newly submitted claim 42 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the invention originally claimed is a
10 polypeptide antagonist of GIP. Claim 42 is directed to a GIP agonist. The antagonist and agonist are structurally and functionally distinct and require separate searches in areas where no pertinent art to the other invention exist.

The originally presented invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 42 is withdrawn from consideration as being
15 directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 1, 8-16, 18-41 are being examined.

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5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

5 In the "APPLICATION FOR A U.S. PATENT TRANSMITTAL FORM" submitted 12/30/97 it is stated that the application claims the benefit under 35 USC 119(e) of U.S. provisional application no. 60/032,329. However, the oath or declaration does not make such a claim. Applicants are required to submit a substitute oath or declaration identifying the provisional application for which claimed benefit is desired.

10 6. A substitute specification including claims is required pursuant to 37 CFR 1.125(a) because the interlineations and/or cancellations made in the specification or amendments to the claims make the application difficult to consider and could lead to confusion and mistake during examination and/or during the issue and printing processes.

15 A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the

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amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

7. Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. A reconstituted antagonist does not infringe a lyophilized antagonist.
8. The amendment filed 04/16/99 (Paper No. 5) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The specification does not provide a basis for a GIP antagonist wherein the GIP antagonist is a fragment of human GIP. The disclosure of human GIP is in the context of immunogenic peptides to be used for the production of antibodies (paragraph bridging pages 7-8). This objection under 35 U.S.C. 132 encompasses the sequence listing, including SEQ ID NOs:4, 6, 13, which are described as human. Deleting "human" would overcome the objection to SEQ ID NOs:4, 6, 13.

Applicant is required to cancel the new matter in the reply to this Office action.

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Claim Rejections - 35 USC § 112

9. Claims 1, 9, 10, 12, 13, 23, 24, 27-32, 35-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. A basis for the following limitations cannot be found in the specification or claims as originally filed: a GIP antagonist comprising a human GIP fragment and/or wherein said human GIP antagonists comprises SEQ ID NOs:2-6, 13; a polypeptide that interferes with the biological activity of GIP wherein said polypeptide comprises an amino acid sequence corresponding to amino acids 16-30, 21-30, or 7-9 of GIP. The introduction of such limitations raises the issue of new matter.

10. Claims 1, 8, 9, 10, 11, 12, 15, 16, 18, 19 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antagonist of GIP consisting essentially of amino acids 7-30 or 10-30 of rat GIP, does not reasonably provide enablement for an antagonist of GIP without regard to the structure thereof, effective alternative sequences thereto, or for antagonistic polypeptides comprising other than amino acids 7-30 or 10-30. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The instant specification clearly contemplates GIP sequences that include additional, deleted or alternative

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amino acids (page 7, lines 14-19). Antagonist that "correspond to" GIP include additional, deleted or alternative amino acids thereto. The specification teaches that rat GIP₇₋₃₀ and 10-30 are antagonist. However, the claims encompass all naturally and non-naturally occurring compounds and/or polypeptides that have the desired activity. The instant specification does not identify those amino acid residues in the amino acid sequence of an antagonist or effective alternative sequences thereto or the structural features of a non-peptide antagonistic compound which are essential for their biological activity and structural integrity and those residues and/or structural features which are either expendable or substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of over 24 amino acid residues and/or random, trial and error testing of all compounds before they could even begin to rationally design a functional antagonist having other than a natural amino acid sequence of rat GIP. The disclosure of a single antagonist with a natural amino acid sequence is clearly insufficient support under 35 U.S.C. § 112, first paragraph, for claims which encompass any and all antagonistic compounds.

The current claim limitations are analogous to those of claim 7 of U.S. Patent No. 4,703,008, which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance a claim to a nucleic acid molecule encoding a

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polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. This limitation is directly analogous to the effective alternative sequences thereto limitation of the instant claims. The disclosure upon which

5 that claim was based described a recombinant DNA encoding EPO and a few analogs thereof.

That disclosure differs from the instant specification because, whereas the instant specification describes a single antagonist with a natural amino acid sequence, it does not describe even a single effective alternative sequence thereto. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention

10 commensurate with the scope of the claims. That means disclosing how to make and use enough sequences to justify the grant of the patent protection sought in the instant claims. As indicated, the instant specification is even more limited than the '008 patent because it describes only a naturally occurring amino acid sequence and no effective alternative sequences thereto and, therefore, provides even less support than the '008 specification for claims of comparable scope

15 and which were held to be invalid in that patent.

The antagonist of claim 39 is only limited by amino acids 7-9 of GIP. The structure of the antagonist is unlimited beyond these three amino acids. The specification has only shown that peptides comprising amino acids 7-30 or 10-30 have antagonistic activity. The specification has not shown that amino acids 7-9 have antagonistic activity. Three amino acids are only ~13% of

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the structure of a 21-24 amino acid peptide. The reasonable expectation in the art would be that deleting 87% of a peptide's structure would result in a non-functional peptide. Moreover, the specification teaches that the peptide antagonists would appear to require amino acids 7-9 and some or all amino acids 10-30. Furthermore, the specification only teaches that the 7-30 and 10-30 fragments are antagonistic (page 13). The specification does not provide a reasonable expectation that peptides other than amino acids 7-30 or 10-30 would have the required activity. The skilled artisan is left to extensive experimentation wherein peptides other than amino acids 7-30 or 10-30 randomly modified and through trial and experimentation is left to determine which peptides are functional. Such extensive, random, trial and error experimentation is considered undue. Moreover, there is a lack of predictability in the art with respect to predicting structure, hence function, from primary amino acid sequence data. See Ngo et al. (U₁₂) wherein it is taught that the native structure of a protein is a unique three-dimensional structure into which the protein folds under physiological conditions and all the information necessary to determine the native structure can be contained in the primary amino acid sequence (page 433, full paragraph 1).

However, it is not even known whether there exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone (page 492, full paragraph 2).

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require

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undue experimentation for the skilled artisan to make and use the full scope of the claimed invention.

11. Claims 11-14, 20, 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing glucose adsorption, does not reasonably provide
5 enablement for preventing, inhibiting, or reducing obesity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to a pharmaceutical composition useful for the preventing, inhibiting, or reducing obesity, which requires that the composition be able to so perform. The specification teaches that ANTIGIP reduced intestinal
10 glucose adsorption (Example 6). However, neither the specification nor the prior art of record establishes a nexus between this activity and preventing, inhibiting, or reducing obesity. The specification fails to disclose specific guidance for administering a GIP antagonist and thereby preventing, inhibiting, or reducing obesity. There are no working examples of preventing, inhibiting, or reducing obesity. Marx (V_{12}) states that few "medical problems have proved to be
15 more intractable than obesity"; the condition is frustratingly hard to treat (page 1477, column 1, full paragraph 1). Woods et al. (W_{12}) teach that although satiety peptides can alter the size of individual meals, their repeated administration does not alter body weight and has limited influence on adiposity (page 1379, column 1, full paragraph 2). In view of the intractable nature

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and unpredictability of treating obesity and the lack of guidance with respect to dosages and the lack of working examples, one skilled in the art could not use claimed pharmaceutical composition for preventing, inhibiting, or reducing obesity without undue experimentation.

12. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being
5 indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is rejected over the recitation of "posts 7-30 of the sequence" because the phrase makes no sense. The metes and bounds of the claim(s) are not clearly set forth.

10 Claims 9, 12, 18, 20, 23, 25, 27, 29, 31, 33, 35, 37 are indefinite over the recitation of "effective number of amino acids" because it is unclear what effect is achieved by the effective number. The metes and bounds of the claim(s) are not clearly set forth.

Claims 9, 10, 12, 13, 18-21, 23-38, 40, 41 are indefinite over the recitation of "effective alternative sequences" because it is unclear what effect is achieved by the effective alternative sequences. The metes and bounds of the claim(s) are not clearly set forth.

15 Claims 11-14, 20, 21 are indefinite because it is unclear if inhibiting, blocking, or reducing glucose adsorption is synonymous with preventing, inhibiting, or reducing obesity or whether some other effect is intended. The metes and bounds of the claim(s) are not clearly set forth.

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Claims 22, 39 are indefinite over the recitation of "effective amount" because it is unclear what effect is intended by an "effective amount"; an intended use is not the same as an effect; in the absence of a recitation as to any effect, or an effective amount of the agent to cause an effect, it is unclear what effect can be inferred.

5 Claims 22-41 are indefinite over the recitation of the acronym "GIP" because its meaning is ambiguous. The acronym could also be formed from the amino acid sequence glycine-isoleucine-proline. It is suggested that the acronym be spelled out at its first occurrence in claims 22 and 39.

10 Claim 36 is indefinite because it is unclear if the polypeptide comprises 10 contiguous or non-contiguous amino acids of the sequence. The metes and bounds of the claim(s) are not clearly set forth.

 The instant specification clearly contemplates GIP sequences that include additional, deleted or alternative amino acids (page 7, lines 14-19). Antagonist that "correspond to" GIP include additional, deleted or alternative amino acids thereto. Claim(s) 1, 9, 10, 12, 13, 18-21, 23-41 are indefinite because they recite the term "corresponding to". Because the instant
15 specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "corresponding to" an artisan cannot determine what additional material and/or functional limitations are placed upon a claim by the presence of this term.

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Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

5 (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 8, 9, 10, 18, 19, 22-41 are rejected under 35 U.S.C. 102(a) as being anticipated
10 by Gelling et al. (X₁₂). The instant application and the 60032329 provisional application only provide a basis for rat ANTIGIP. Gelling et al. teach porcine GIP_{10-30, 6-30, 7-30} antagonistic peptides (Abstract). Porcine GIP₇₋₃₀ consist essentially of a 24 amino acid polypeptide corresponding to positions 7-30 of the sequence of human GIP, SEQ ID NO:2. Porcine GIP_{10-30, 6-30, 7-30} comprise at least an effective number of amino acids corresponding to those amino acids in
15 the 7-30 positions of human or rat GIP, SEQ ID NO:2 or 8, respectively, or effective alternative sequences thereto. Porcine GIP₆₋₃₀ comprises at least an effective number of amino acids corresponding to those amino acids in the 7-30 positions of rat GIP, SEQ ID NO:8, or effective alternative sequences thereto. A chemical composition and its properties are inseparable. Therefore, the properties applicant discloses and/or claims, i.e. "interferes with the biological

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activity of GIP in an animal", are an inherent property of Porcine GIP_{10-30, 6-30, 7-30}. Porcine GIP₆₋₃₀ is an effective alternative sequence to amino acids 16-30 of rat GIP, SEQ ID NO:9.

15. Claims 1, 8-14, 18-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Ebert et al. (Y₁₂). Ebert et al. teach a specific GIP antiserum (page 1601, paragraph bridging columns 1-2). The antiserum comprises an antibody or antibodies that is or are an antagonist of GIP, consist essentially of or comprise a 24 amino acid polypeptide corresponding to any position of the sequence of GIP or comprise at least an effective number of amino acids corresponding to those amino acids in any position of GIP or effective alternative sequences thereto. Ebert et al. also teach a pharmaceutical composition comprising the anti-GIP, antagonistic antibody or antibodies (page 1602, columns 1-2). Inhibiting, blocking, or reducing glucose adsorption from the intestine is an inherent property of the antibody or antibodies, absent any evidence to the contrary. The intended use of the claimed pharmaceutical composition has not been given patentable weight because the recitation occurs in the preamble.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 8, 15, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelling et al. (X₁₂) or Ebert et al. (Y₁₂) as applied to claim 8 above, and further in view of Avis (Z₁₂) and/or Turco (UU₁₂). Gelling et al. or Ebert et al. teach a GIP antagonist, as discussed above. Gelling et al. or Ebert et al. are silent with respect to a lyophilized and/or reconstituted GIP antagonist.

Avis teaches that biologics and pharmaceuticals can be stored in the dry state in which there are relatively few stability problems (page 1565, paragraph bridging columns 1-2). Turco teaches that proper electrolyte concentration and balance in plasma and tissues are critical for proper body function and that the electrolytes in normal saline more closely approximate the composition of the extracellular fluid than solutions of any other single salt (page 1570, column 2, bottom). Avis and/or Turco are silent with respect to a lyophilized and/or reconstituted GIP antagonist.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a GIP antagonist, as taught by Gelling et al. or Ebert et al., and to modify that teaching by lyophilizing and/or reconstituting the antagonist, as taught by Avis and/or Turco, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because there are relatively few stability problems in the dry state and because normal saline more closely approximates the composition of the extracellular fluid than solutions of any other single salt. The invention is prima facie obvious over the prior art.

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Conclusion

18. No claims are allowable.


5 Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

10 Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


DAVID ROMEO
PATENT EXAMINER
January 12, 2000

Notice of References Cited

Application No.
09/121,211

Applicant(s)
Shinohara et al.

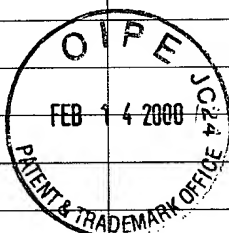
Examiner
David S. Romeo

Group Art Unit
1646

Page 1 of 1

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A	5,604,293	2/1997	Fiddes et al.	530	399
B					
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					



FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
U	Sambrook et al. Molecular Cloning: A Laboratory Manual Second Edition Vols. 1, 2 and 3. Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York, U.S.A. November, 1989, page 9.50.	11/1989
V	Database Medline on STN, Medline Accession No. 1999366075, US National Library of Medicine, Bethesda, MD, USA, Li et al. Promotive effects of basic fibroblast growth factor on proliferation of bovine lens epithelial cells. Chung-hua Yen Ko Tsa Chih [Chi	3/1997
W	Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, Merz and Le Grand (Eds), August 1994, Springer Verlag, pages 433 and 492-495.	11/1989
X		

David S. Romeo 01/24/00